Oxytrol® for Women

(Oxybutynin Transdermal System (TDS) 3.9 mg

Andrea Leonard-Segal, M.D., M.S.
Director, Division of Nonprescription Clinical Evaluation

Overview

- Merck Consumer Care submitted a new drug application to partially switch Oxytrol® from prescription (Rx) to over-the-counter (OTC)
  - Approved Rx product since 2003 to treat overactive bladder with symptoms of urge urinary incontinence, urgency and frequency
  - Proposed OTC use is "treats overactive bladder in women"
    - Age ≥ 18 years
  - Product would remain Rx for men

Overview

- Among other information, presentations will include
  - Review of postmarketing data
  - Results of consumer studies (label comprehension, self-selection, and an actual use study) conducted to support the switch application
- We are asking the Committee to consider whether the data support the appropriate and safe use of the oxybutynin TDS by OTC consumers

Agenda

- 8:25 a.m. **Merck Consumer Care Presentations**
- 9:40 a.m. Clarifying Questions
- 10:05 a.m. **Break**
- 10:20 a.m. **FDA Presentations**
- 11:35 a.m. Clarifying Questions
- 12:00 p.m. **Lunch**
- 1:00 p.m. **Open Public Hearing**
- 2:00 p.m. Questions to the Committee/Committee Discussion
- 3:00 p.m. **Break**
- 3:15 p.m. Questions to the Committee/Committee Discussion
- 5:00 p.m. **Adjourn**

Overview of the Efficacy and Safety Database for NDA 21-351

Oxytrol (oxybutynin transdermal system [TDS])

Donald McNellis, MD
Division of Reproductive and Urologic Products

Nonprescription Drugs Advisory Committee Meeting
November 9, 2012

Overactive Bladder (OAB) - Definition

A symptom complex that occurs in men and women and consists of urinary urgency, with or without urgency incontinence, usually with urinary frequency and nocturia, in the absence of other local or metabolic factors that would account for the symptoms

- OAB has a negative effect on quality of life, even when controlling for co-morbid conditions

Conditions With Symptoms Potentially Similar to Those of Overactive Bladder

- Diabetes
- Bladder cancer
- Urinary tract infection
- Pregnancy
- Prostate disease in men

Prevalence of OAB

- In population-based studies, OAB prevalence rates range from 7% to 27% in men, and 9% to 43% in women.
- Some studies report higher prevalence rates in women than men, while others found similar rates across genders. However, urgency urinary incontinence is consistently more common in women than in men.
- OAB symptom prevalence and severity tend to increase with age.

Initial Management of OAB

- Life Style Interventions
  - Limit fluid intake
  - Avoid beverages with caffeine or alcohol
- Bladder Retraining
  - Extend the period of time between voids in an attempt to re-establish inhibitory influence

Approved Pharmacotherapy for Treatment of OAB

- Oxybutynin products
  - ***Transdermal Oxybutynin Patch (Oxytrol TDS)***
  - Oxybutynin Gel
  - Oxybutynin tablets and syrup
- Other anti-muscarinic products
  - Tolterodine
  - Trospium
  - Darifenacin
  - Solafenacin
  - Fesoterodine
- Beta-3 receptor agonist product
  - Mirabegron

Oxytrol Transdermal System

- Approved on February 26, 2003
- Dose: 3.9 mg/day patch is applied twice weekly
- Indication: For the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency

Clinical Trials Efficacy Database

The Application was Supported by Two Phase 3, Placebo Controlled, Randomized, Double-Blind Clinical Trials

- ***O99009*** – 12 week trial evaluating 3 doses of Oxytrol (including the 3.9 mg/day) and placebo
  - Primary endpoint - Change from baseline in number of **weekly** incontinence episodes

- ***O00011*** – 12 week trial evaluating Oxytrol (3.9 mg/day), tolterodine, and placebo.
  - Primary endpoint - Change from baseline in number of **daily** incontinence episodes

Efficacy Results for Trial O99009

Parameter	Placebo (N=127)		Oxytrol 3.9 mg/day (N=120)	
	Mean (SD)	Median	Mean (SD)	Median
Weekly Incontinence Episodes				
Baseline	37.7 (24.0)	30	34.3 (18.2)	31
Reduction	19.2 (21.4)	**15**	21.0 (17.1)	**19**
p value vs placebo	-		**0.0265**	
Daily Urinary Frequency				
Baseline	12.3 (3.5)	11	11.8 (3.1)	11
Reduction	1.6 (3.0)	**1**	2.2 (2.5)	**2**
p value vs placebo	-		**0.0313**	
Urinary Void Volume (ml)				
Baseline	175.9 (69.5)	166.5	171.6 (65.1)	168
Increase in Vol. (cc)	10.5 (56.9)	**5.5**	31.6 (65.6)	**26**
p value vs placebo	-		**0.0009**	

Efficacy Results for Trial O00011

Parameter	Placebo (N=127)		Oxytrol 3.9 mg/day (N=120)	
	Mean (SD)	Median	Mean (SD)	Median
Daily Incontinence Episodes				
Baseline	5.0 (3.2)	4	4.7 (2.9)	4
Reduction	2.1 (3.0)	**2**	2.9 (3.0)	**3**
p value vs placebo	-		**0.0137**	
Daily Urinary Frequency				
Baseline	12.3 (3.3)	12	12.4 (2.9)	12
Reduction	1.4 (2.7)	**1**	1.9 (2.7)	**2**
p value vs placebo	-		**0.1010**	
Urinary Void Volume (ml)				
Baseline	175.0 (68.0)	171.0	164.8 (62.3)	160
Increase in Vol. (cc)	9.3 (63.1)	**5.5**	32.0 (55.2)	**24**
p value vs placebo	-		**0.0010**	

Efficacy Conclusions

- Oxytrol Transdermal System [TDS] (3.9 mg/day) achieved the primary efficacy objective, reduction in incontinence episodes, in both phase 3 trials.

- Reduction in urinary frequency was statistically significant as compared to placebo in trial O99009, but not in trial O00011.

- Increase in void volume was statistically significant as compared to placebo in both trials.

Clinical Trial Safety Database

- Supported by 16 phase 1, 1 phase 2, and 2 phase 3 trials

- Approximately 600 subjects were exposed for periods of 1 – 428 days. The average exposure was 150 days.

Deaths

- No deaths were reported during clinical trials
  - Two patients died from causes believed to be unrelated to study medication: One death occurred prior to the patient initiating Oxytrol treatment, and the other, following completion of study participation.

Serious Adverse Events (SAEs)

- During Clinical Development 37 subjects experienced a total of 47 SAEs.
- None of the SAEs were considered to be related to Oxytrol
- 9 patients discontinued trials early because of SAEs

Summary of Adverse Events Seen in >1% of Subjects in the Phase 3 Trials

Preferred Term	Number of Events (%)	
	Placebo Containing TDS N=249	Oxytrol TDS 3.9 mg/day N=246
Application Site Pruritis	13 (5.2%)	38 (15.4%)
Application Site Erythema	5 (2.0%)	17 (6.9%)
Dry Mouth	13 (5.2%)	17 (6.9%)
Application Site Vesicles	0	7 (2.8%)
Diarrhea	3 (1.2%)	4 (1.6%)
Constipation	0	4 (1.6%)
Dysuria	0	3 (1.2%)
Abnormal Vision	0	3 (1.2%)

Safety Conclusions

- Major safety issues reported during clinical trials included: skin tolerability and anticholinergic side effects (such as dry mouth and constipation).

- No safety issues were identified that precluded Oxytrol TDS approval.

Additional Considerations

Timing of Symptom Improvement

- In both phase 3 clinical trials, the primary endpoint was shown to be significantly improved in the Oxytrol cohort as compared to the placebo cohort at the first on-treatment visit.
- This efficacy was maintained through the 12 week trial.
- The first visit occurred at Week 3 in trial 09 and at Week 2 in trial 11.

Pregnancy

- Oxytrol is labeled as Pregnancy Category B

- This classification has not been a deterrent to the switch of other prescription drugs to OTC status

Contraindications to Oxytrol Use

- Urinary retention
- Gastric retention
- Uncontrolled narrow-angle glaucoma
- Known serious hypersensitivity reaction to OXYTROL, oxybutynin, or to any of the components of OXYTROL

Oxytrol – Warnings and Precautions

These are drug class-effects and are not based on any specific safety signals seen with Oxytrol

- Risk of urinary retention
- Risk of gastric retention
- Risk of exacerbation of esophagitis in patients with GI reflux
- Potential CNS effects including dizziness and somnolence
- Angioedema has been reported with oral oxybutynin use
- Skin hypersensitivity
- Use with caution in patients with myasthenia gravis

Oxytrol for Women ® Label Comprehension and Self-Selection Consumer Research

Presentation to Nonprescription Drugs Advisory Committee
November 9, 2012

Barbara R. Cohen, MPA
Social Science Analyst

Outline:

- Overview of Label Comprehension and Self Selection
- Key Medical Issues Addressed in Consumer Research (Label)
- Other Important Medical Issues Addressed (Label)
- Summary of “Good News”
- Summary of Caveats and Research Gaps
- Sponsor’s Proposed Labeling Changes
- Recommendations for Labeling Enhancements

Label Comprehension Studies

- **Pivotal Label Comprehension – conducted in late 2010 – most recent.**
- General OAB age 65+ - *conducted in early 2010.*
- Diabetic Warnings - General OAB Sufferers – *conducted in early 2010.*
- Enhanced Pregnancy Warning Among Women of Childbearing Age – *conducted in early 2010.*
- Normal/Low literacy female OAB Sufferers, General Female Non-OAB sufferers, Men – *conducted in 2008.*

Self-Selection Studies

- Self-selection in pregnant women – *conducted in late 2010.*
- Self-selection in men – *conducted in late 2009.*
- Self-selection – *conducted in early 2009.*
  - Normal/low lit with OAB symptoms.
  - Four other subpopulations – men, diabetics, glaucoma, pregnant/nursing.

Label Comprehension and Self-Selection

- Label comprehension – do consumers understand what the label says when they are asked to focus on it?

- Self-selection – how might consumers apply what they take away from the label to their own personal situation?

Label Comprehension – Typical Design

- Establish primary communications objectives based on unique key labeling elements.
- Ask scenario questions that address these communications objectives.
- Set – a priori – target thresholds that reflect medical consequence/risk considerations.
  - Target thresholds are a clinical judgment call. They are by nature subjective – though there is an underlying clinical rationale.
  - Target thresholds not the same as traditional clinical trial success thresholds.

Target Thresholds

- Measure *lower bound* of 95% confidence interval against target thresholds.
  - Therefore, a conservative estimate.

Pivotal LCS – Target Thresholds

- Target thresholds were established by the Sponsor for each objective based on level of medical consequences if not understood.
- Some objectives were at 90% - higher medical consequences.
- Some objectives were at 85% - lower medical consequences.

Definition of Terms

- LB – Lower Bound of Confidence Interval
  - Results here will be reported that way, unless otherwise specified.
  - Point estimates when comparing normal literacy and low literacy.
- NL – Normal literacy
- LL – Low literacy
- LCS – Label Comprehension Study
- OAB – Overactive bladder

Key Medical Issues

- Major medical concerns discussed between FDA and Sponsor from 2007-2011:
  - Consumer identification of OAB
  - Urinary/gastric retention
  - Diabetes Risk
  - UTI
  - Pregnant Women
  - Men
  - Elderly

Key Medical Issues

- **Consumer identification of OAB**
- Urinary/gastric retention
- Diabetes Risk
- UTI
- Pregnant Women
- Men
- Elderly

Pivotal LCS – Correct Identification of OAB

- **Communication objective tested:**
  - You may be suffering from overactive bladder if you have had two or more of the following symptoms for at least three months:
    - Urinary frequency (the need to urinate more often than usual; typically more than 8 times in 24 hours)
    - Urinary urgency (a strong need to urinate right away)
    - Urge incontinence (leaking or wetting yourself if you cannot control the urge to urinate)

Pivotal LCS – Correct Identification of OAB

- This communication objective was split into two questions.
- Only one question– pertaining to symptom duration – was measured against a target threshold. (85% - lower level of medical risk)
- The other question – pertaining to symptom identification – was not measured against a target threshold.

Pivotal LCS: Correct Identification of OAB – Question "A"

- According to the label, for how long should you have symptoms of overactive bladder before trying the product?

Pivotal LCS – Correct Identification of OAB – Question "A"

- Comprehension of OAB symptoms for 3+ months within 1 point of 85% target threshold – at 84% LB.
  - By far the largest percentage of "don't knows" in the survey findings - at 8%.
  - 88% NL v 71% LL (point estimates)
  - Also tested in earlier "*Age 65+ Label Comprehension Study*" – 74% LB.

Pivotal LCS: Correct Identification of OAB – Question "B"

- For the past 4 months, Betsy has had to urinate more often than usual, about 9 times every 24 hours. She has also had several leaking accidents. She has no other medical conditions. Betsy would like to use this product. Is it okay or not okay for Betsy to use this product?
  - Since everything in the above scenario was more than what the label indicated, the question did not measure the ability of consumers to comprehend when a scenario was incorrect.

Pivotal LCS: Correct Identification of OAB – Question "B"

- Question B was not measured against a target threshold; nonetheless, the data on comprehension are available:
  - Cohort 1 – LB 82%.
  - In two previous label comprehension studies with a 2 week scenario (and the same label), consumers had much lower levels of comprehension.
  - Therefore, results may be best case.

Key Medical Issues

- Consumer identification of OAB
- **Urinary/gastric retention**
- Diabetes Risk
- UTI
- Pregnant Women
- Men
- Elderly

Pivotal LCS – Urinary Retention and Gastric Retention

- **Communication objectives tested:**
  - Do not use if you have urinary retention (are not able to empty your bladder)
  - Do not use if you have been told by a doctor that you have gastric retention (your stomach empties slowly after a meal)

Pivotal LCS – Gastric Retention

- LB 87% - 3 points below 90% (higher level of medical risk) target threshold:
  - 91% NL vs 74% LL (point estimates).
  - Note: In previous "*Age 65+ Label Comprehension Study*," LB was 81%.
  - Gastric retention may have more resonance with those who have been told they have it.

Pivotal LCS – Urinary Retention

- LB 88% – 2 points below 90% (higher level of medical risk) target threshold.
  - Note: In previous *Age 65+ Label Comprehension Study*, LB was 83%.

- Label was subsequently revised to reflect a diagnosis by a doctor.

Key Medical Issues

- Consumer identification of OAB
- Urinary/gastric retention
- **Diabetes Risk**
- UTI
- Pregnant Women
- Men
- Elderly

Pivotal LCS – Diabetes Risk (Cohort 3)

- **Communication objective tested:**

  Ask a doctor before use if you have a family history or frequent urination with excessive thirst, extreme hunger or increased tiredness.

  – This was split into two questions.
  – Target threshold of each question set at 85% (lower medical risk).
  – However, it still wasn't completely addressed.

Pivotal LCS: Diabetes Risk - Question “A”

- For the past 5 months, Megan has had to urinate frequently and urinate right away. Her mother has diabetes. Megan would like to use this product. According to the label, what, if anything, should Megan do?

Pivotal LCS – Diabetes Risk - Question "A"

- Comprehension of diabetes risk – LB 83% - 2 pts below threshold:
  - 91% NL vs 72% LL (point estimates)
  - Earlier "*Age 65+ Label Comprehension Study*" – 88% LB.
  - Earlier "*Diabetic Warnings among General Population Label Comprehension Study*" – 90% LB.

Pivotal LCS: Diabetes Risk - Question “B”

- Rachel has been experiencing excessive thirst. She also noticed that she has been needing to urinate more often than usual. Rachel would like to use this product. According to the label, what, if anything, should Rachel do?

Pivotal LCS – Diabetes – Question "B"

- Comprehension of diabetes risk – LB 82% - 3 pts below threshold.
  - 90% NL vs 72% LL (point estimates)
- "*Age 65+ Label Comprehension Study*" (wasn't asked).
- "*Diabetic Warnings Among General Population Label Comprehension Study*" – LB 92%:
  - 91% NL vs 71% LL (point estimates)

Pivotal LCS – Diabetes Risk

- Neither question incorporated extreme tiredness or hunger, although these were stated communications objectives and also on the labeling.
- Also not incorporated in other studies.

Key Medical Issues

- Consumer identification of OAB
- Urinary/gastric retention
- Diabetes Risk
- **UTI**
- Pregnant Women
- Men
- Elderly

Pivotal LCS - UTI

- Sponsor determined that this was not a communications objective for the pivotal.

- No questions in pivotal LCS about any common UTI symptoms such as pain, burning or cloudy urine.

Age 65+ LCS - UTI

- Comprehension of not ok to use if blood in urine – LB at 94%.
- Comprehension of not ok to use if pain while urinating – LB at 93%.
- Comprehension of not ok if foul smelling urine – LB at 88%.
- Comprehension of not ok if pain in lower back – LB at 89%.

LCS: NL OAB and General Non OAB Sufferers - UTI

- Comprehension of not ok to use if blood in urine:
  - LB 89% NL OAB, 91% non-OAB
- Comprehension of not ok to use if pain while urinating:
  - LB 87% NL OAB, 93% non-OAB
- Comprehension of not ok if pain in lower back:
  - LB 91% NL OAB, 90% non-OAB

Key Medical Issues

- Consumer identification of OAB
- Urinary/gastric retention
- Diabetes Risk
- UTI
- **Pregnant Women**
  - **Unknown Pregnancy (LCS)**
  - **Known Pregnancy (Self-Selection)**
- Men
- Elderly

Pivotal LCS - Pregnancy

- No questions on this in the pivotal LCS.

Enhanced Pregnancy Warning LCS: Unknown Pregnancy

- **Communication Objective Tested**:
  - If you need to urinate frequently it could be a sign of pregnancy, diabetes, a urinary tract infection (UTI) or a more serious condition. If you think you could have one of these conditions, it is important to see a doctor before using this product.

- Question:
  - Melissa has noticed that she has had to urinate more frequently. She also has noticed that she has missed two periods. Melissa thinks this product may help with her more frequent urination. According to the label, what if anything should Melissa do?

Enhanced Pregnancy Warning LCS: Unknown Pregnancy

- LB 90% said Melissa should talk to a doctor.
  - "Two" missed periods cuing response?

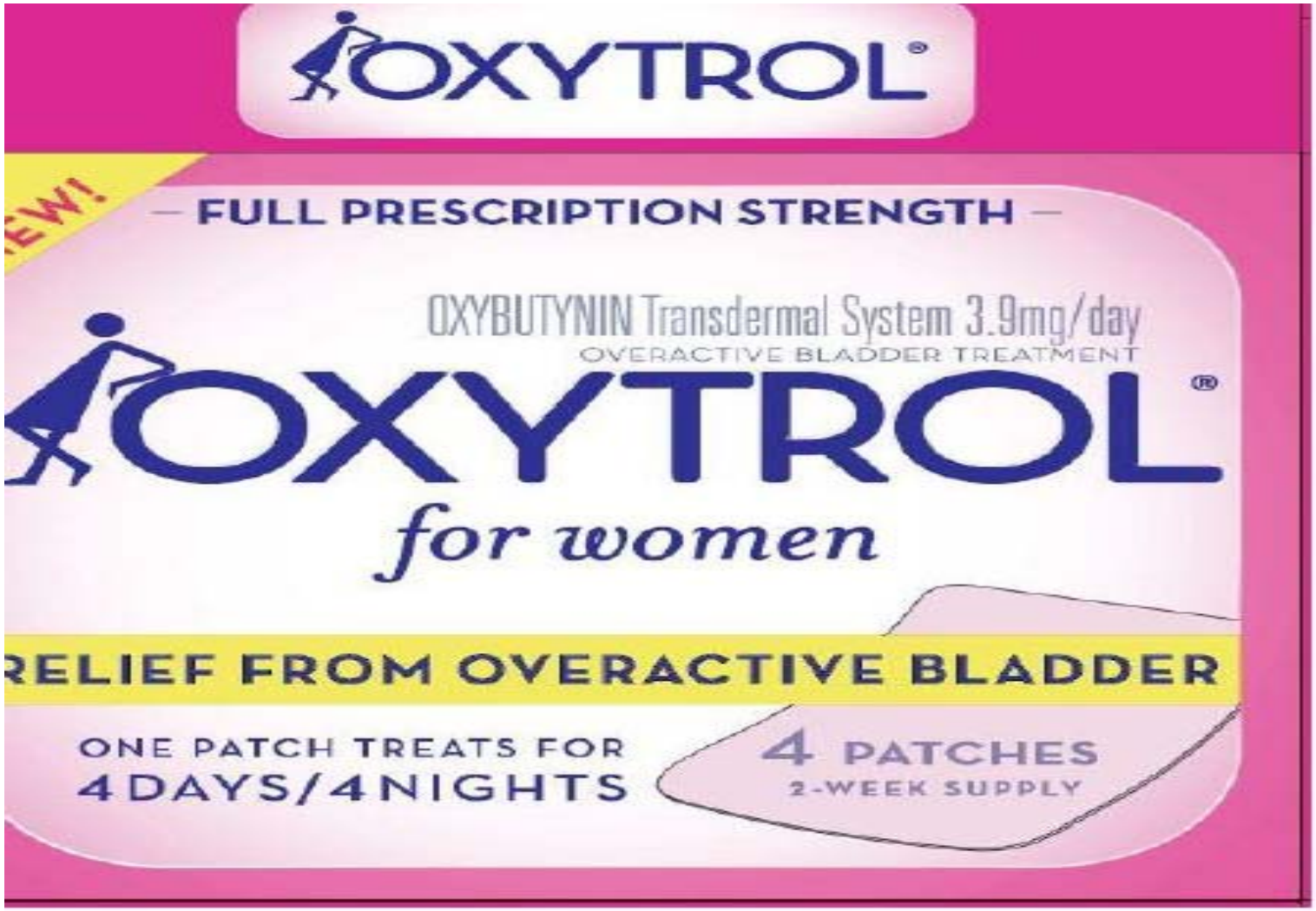
Self-Selection: Known Pregnancy

- Self-Selection study with pregnant women with OAB symptoms:
  - N=435
  - Study participants given a copy of the label to read.
  - Asked: Do you believe this product is appropriate to use right now, or not? Why do you say that? What led you to that decision?

Self-Selection: Known Pregnancy

- Self-Selection study with pregnant women with OAB symptoms:
  - Did not meet primary endpoint of 90% - LB of 84%. Sponsor mitigated to 88%.
  - Low literacy – LB of 54%. Sponsor mitigated to 68%.
  - Mitigations based on challenge questions involving a third probe.
  - Majority of those making incorrect self-selection decisions focused on the symptoms rather than the warning.
  - Label drawing revised to emphasize woman with slender silhouette.

Self-Selection in Pregnant Women - Label



Current Proposed Label

Key Medical Issues

- Consumer identification of OAB
- Urinary/gastric retention
- Diabetes Risk
- UTI
- Pregnant Women
- **Men**
- Elderly

Pivotal LCS – Men

- No questions on this in the pivotal LCS.

Self-Selection: Men

- Self-Selection study with men with OAB symptoms:
  - N=571
  - Study participants given a copy of the label to read.
  - Asked: Do you believe this product is right for YOU to use? Why do you say that? What led you to that decision?

Self-Selection: Men

- Self-selection study targeted to men:
  - The lower bound (88%) fell below the 90% threshold.
  - Low literacy cohort scored approximately the same as normal literacy.
  - 62% of incorrect selectors focused on urinary symptoms only.

Key Medical Issues

- Consumer identification of OAB
- Urinary/gastric retention
- Diabetes Risk
- UTI
- Pregnant Women
- Men
- **Elderly**

Age 65+: Pivotal LCS and Age 65+ LCS

- Generally there were no statistically significant differences in pivotal study between age 60+ and under 60.

- Generally in "*Age 65+ Label Comprehension Study*" comprehension was from LB 85% and up.

Pivotal LCS - Other Communication Objectives – Higher Medical Risk (90%)

- Not ok to use if allergic to oxybutynin – LB 93%.
- Stop use and ask a doctor if allergic reaction – LB 91%.
- Stop use and ask a doctor if developed blisters and red/itchy rash – LB 85%.
- Not ok to use if have narrow angle glaucoma – LB 84%.
  - 1st generation OTC antihistamines have glaucoma warning on label.

Pivotal LCS – Other Communications objectives - Lower Medical Risk – 85%

- Ask a doctor – kidney stones – LB 87%.
- Ask a doctor, has liver disease – LB 80%.
- Not ok to use, stress incontinence – LB 73%

The Good News

General Population Findings:

- Most communications objectives scored within a few points of a priori target thresholds – if not above. Most were at 80% or above.

- Age 65+ did not have significantly lower comprehension on most labeling elements than younger consumers.

NL vs LL Findings:

- LL findings – though lower than NL as anticipated – were not atypical or unusually low in the pivotal.

Caveats

General Population Findings:

- Potential for upward bias in findings.
  - Question wording:
    - Pregnancy (LCS and Self-Selection)
  - LL representation in general population was sub-optimal.
    - Ranged from pivotal at 6% to self selection in men at 16%.

Research Content Area Gaps

- Comprehension testing on consumer OAB identification had limitations.
- Comprehension of extreme tiredness/hunger as diabetes symptoms not assessed.
- No assessment of UTI comprehension in female OAB general population.

Sponsor's Proposed Labeling Changes

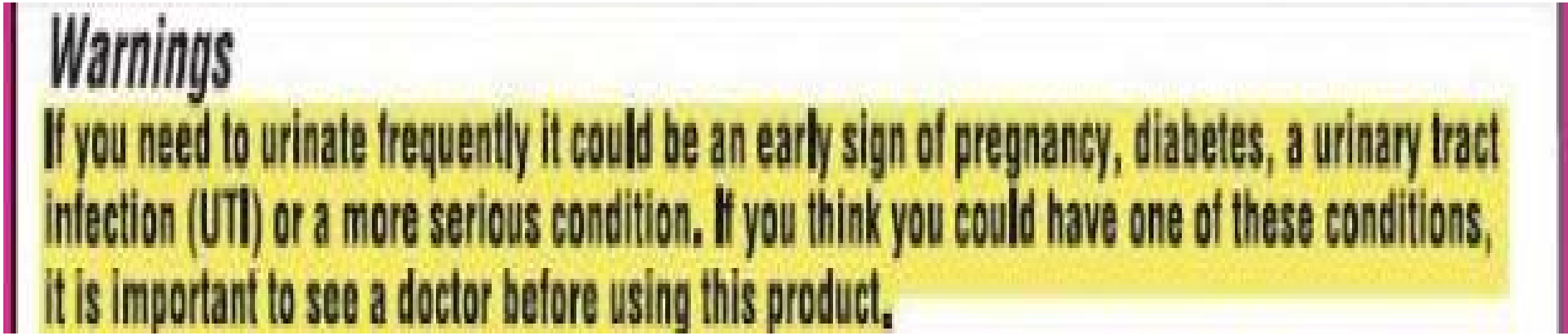
- **Underlying conditions listed in the "Warnings" section have been bulleted to further emphasize.**

- Further emphasized UTI symptoms through placement, bulleting and wording.

- Added symptoms of urinary retention to "Stop Use and Ask a Doctor" section.

- Bulleted diabetes symptoms in "Ask a Doctor Before Use section."

Pivotal LCS - Label



Warnings

If you need to urinate frequently it could be an early sign of pregnancy, diabetes, a urinary tract infection (UTI) or a more serious condition. If you think you could have one of these conditions, it is important to see a doctor before using this product.

Current Proposed Label

Warnings

Frequent urination can also be caused by:

■ urinary tract infections (UTI) ■ diabetes ■ early pregnancy ■ other more serious conditions

If you think you might have one of these conditions, see your doctor before use.

Sponsor's Proposed Labeling Changes

- Underlying conditions listed in the "Warnings" section have been bulleted to further emphasize.

- **Further emphasized UTI symptoms through placement, bulleting and wording.**

- Added symptoms of urinary retention to "Stop Use and Ask a Doctor" section.

- Bulleted diabetes symptoms in "Ask a Doctor Before Use section."

Pivotal LCS - Label

Do not use if you

- are male
- are under the age of 18
- **have <u>any</u> of the following symptoms:**
  - pain or burning when urinating. These symptoms may also be accompanied by a fever or chills.
  - blood in your urine
  - lower back or side pain
  - urine that is cloudy or foul-smelling

these symptoms could be the sign of a serious condition and you should see your doctor as soon as possible.

Current Proposed Label

Do not use if you

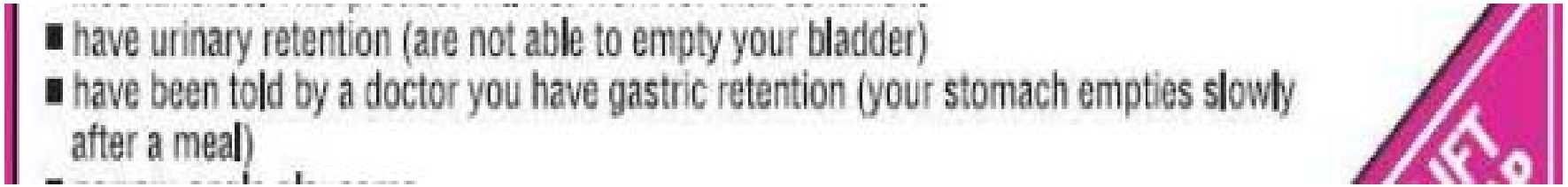
- **have any of these symptoms, which could be the sign of a UTI or other serious condition. See your doctor as soon as possible if you have:**
  - pain or burning when urinating. These symptoms may also be accompanied by a fever or chills.
  - blood in your urine
  - unexplained lower back or side pain
  - urine that is cloudy, or foul-smelling

Sponsor's Proposed Labeling Changes

- Underlying conditions listed in the "Warnings" section have been bulleted to further emphasize.
- Further emphasized UTI symptoms through placement, bulleting and wording.
- **Added symptoms of urinary retention to "Stop Use and Ask a Doctor" section.**
- Bulleted diabetes symptoms in "Ask a Doctor Before Use section."

Pivotal LCS - Label

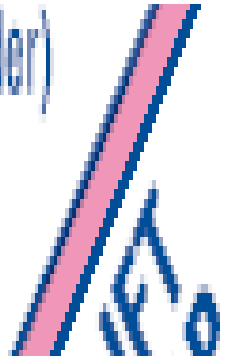
- Do not use if you:



Current Proposed Label

Do not use if you:

- have been told by a doctor you have urinary retention (are not able to empty your bladder)
- have been told by a doctor you have gastric retention (your stomach empties slowly after a meal)



Pivotal LCS - Label

Stop use and ask doctor if

- condition worsens, or if new symptoms appear
- condition does not improve after 2 weeks of use
- you have an allergic reaction to this product
- you have severe redness, itchiness or blistering at the site of application

Current Proposed Label

Stop use and ask a doctor if

- you are not able to empty your bladder (urinary retention)
- condition worsens, or if new symptoms appear
- condition does not improve after 2 weeks of use
- you have an allergic reaction to this product
- you have severe redness, itchiness or blistering at the site of application

Sponsor's Proposed Labeling Changes

- Underlying conditions listed in the "Warnings" section have been bulleted to further emphasize.
- Further emphasized UTI symptoms through placement, bulleting and wording.
- Added symptoms of urinary retention to "Stop Use and Ask a Doctor" section.
- **Bulleted diabetes symptoms in "Ask a Doctor Before Use section."**

Pivotal LCS - Label

Ask a doctor before use if you have

- a history of diabetes in your immediate family
- frequent urination with excessive thirst, extreme hunger or increased tiredness. These could be early signs of diabetes.
- unexplained weight loss
- a history of kidney stones
- liver or kidney disease

Current Proposed Label

Drug Facts (continued)

Ask a doctor before use if you have

- risk factors or symptoms of diabetes, such as:
  - a history of diabetes in your immediate family
  - excessive thirst
  - extreme hunger
  - increased tiredness
- unexplained weight loss
- a history of kidney stones
- liver or kidney disease

Social Science Labeling Recommendations for Consideration

- **Enhance "at least" in the phrase "at least three months" to make it stand out more in a section that cites various numbers.**

- Separate out diabetes risk factors from diabetes symptoms to make each stand out more.

- Add back into the label the *importance* of seeing a doctor into the UTI section. This was in an earlier version and was removed.

Current Proposed Label

Use

- treats overactive bladder in women
- you may be suffering from overactive bladder if you have had 2 or more of the following symptoms for at least 3 months:
  - urinary frequency (the need to urinate more often than usual; typically more than 8 times in 24 hours)
  - urinary urgency (a strong need to urinate right away)
  - urge incontinence (leaking or wetting yourself if you cannot control the urge to urinate)

Social Science Labeling Recommendations for Consideration

- Enhance “at least” in the phrase “at least three months” to make it stand out more in a section that cites various numbers.

- **Separate out diabetes risk factors from diabetes symptoms to make each stand out more.**

- Add back into the label the *importance* of seeing a doctor into the UTI section. This was in an earlier version and was removed.

Current Proposed Label

Drug Facts (continued)

Ask a doctor before use if you have

- risk factors or symptoms of diabetes, such as:
  - a history of diabetes in your immediate family
  - excessive thirst
  - extreme hunger
  - increased tiredness
- unexplained weight loss
- a history of kidney stones
- liver or kidney disease

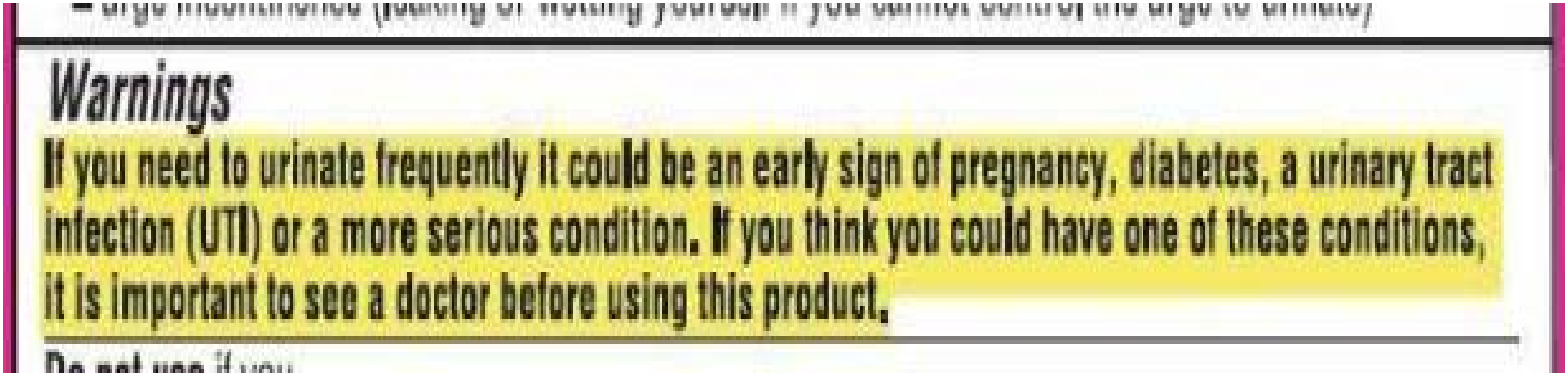
Social Science Labeling Recommendations for Consideration

- Enhance “at least” in the phrase “at least three months” to make it stand out more in a section that cites various numbers.

- Separate out diabetes risk factors from diabetes symptoms to make each stand out more.

- **Add back into the label the *importance* of seeing a doctor into the UTI section. This was in an earlier version and was removed**.

Pivotal LCS - Label



Warnings

If you need to urinate frequently it could be an early sign of pregnancy, diabetes, a urinary tract infection (UTI) or a more serious condition. If you think you could have one of these conditions, it is important to see a doctor before using this product.

Current Proposed Label

Warnings

Frequent urination can also be caused by:

- urinary tract infections (UTI)
- diabetes
- early pregnancy
- other more serious conditions

If you think you might have one of these conditions, see your doctor before use.

Oxytrol for Women® - The Clinical Perspective

Sponsor: MSD Consumer Care

Nonprescription Drug Advisory Committee Meeting
Silver Spring, MD
November 9, 2012

Ryan Raffaelli, M.D., Medical Reviewer
Division of Nonprescription Clinical Evaluation

OUTLINE

- Briefly describe the Actual Use Study design
  - Discuss
    - Purchase decisions and label ineligibility
    - Primary and secondary endpoints
- Primary safety topics and label ineligibilities
- Prescription Oxytrol® postmarketing experience

Consumer Trial of Oxytrol® (CONTROL)

Design of CONTROL

- Open-label, single-arm, multicenter trial (26 pharmacy sites)
  - Typical of Actual Use Studies (AUS)
  - Predict, in a "naturalistic" OTC setting, how consumers might use the drug
- Purpose: Assess use and misuse
- Major endpoints: Misuse rates (also typical of AUS)

  ****Primary endpoint**: new or worsening symptoms (labeled) reported by any user of at least one TDS over the duration of the trial**
  - Secondary endpoint 3: no improvement of OAB symptoms after 2 weeks
  - Secondary endpoint 5: incorrect use by prolonged duration (> 4 days) or simultaneous use of more than one TDS
- Duration: 12 week use phase
  - 88% of all users completed the week 12 interview

Design of CONTROL

- Methods
  - Recruitment/Screening
  - Enrollment
  - Use
    - "At home" use
  - Evaluation
    - Interviews (weeks 3, 7, 12)
      - Scripts were adequate
    - Diaries
    - EOS urinalysis and EOS interview
      - Urinalysis: 58% of users
      - Interview: 82% of all dispensed drug

Exclusion Criteria:

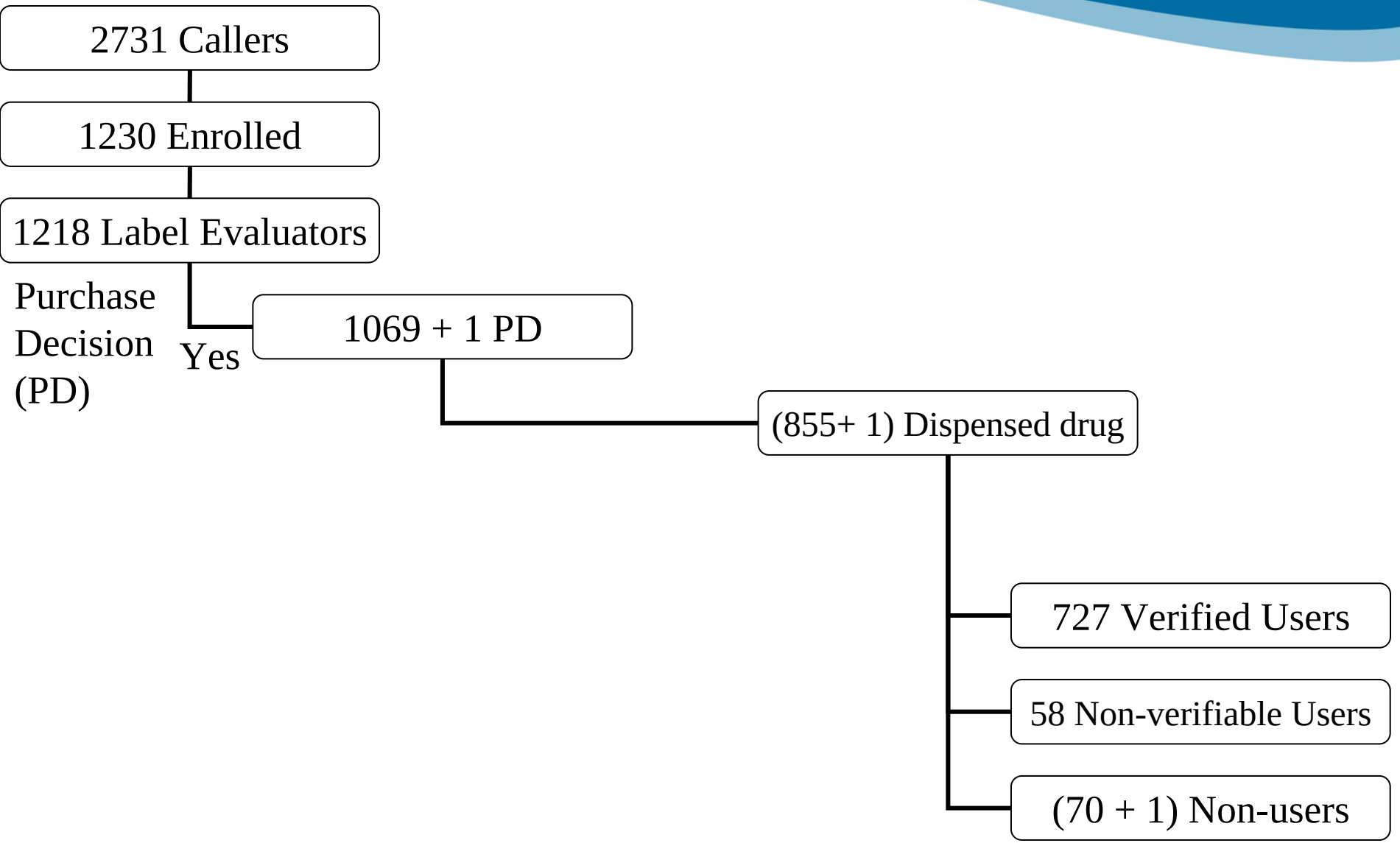
- Male
- Under age 18

} At screening

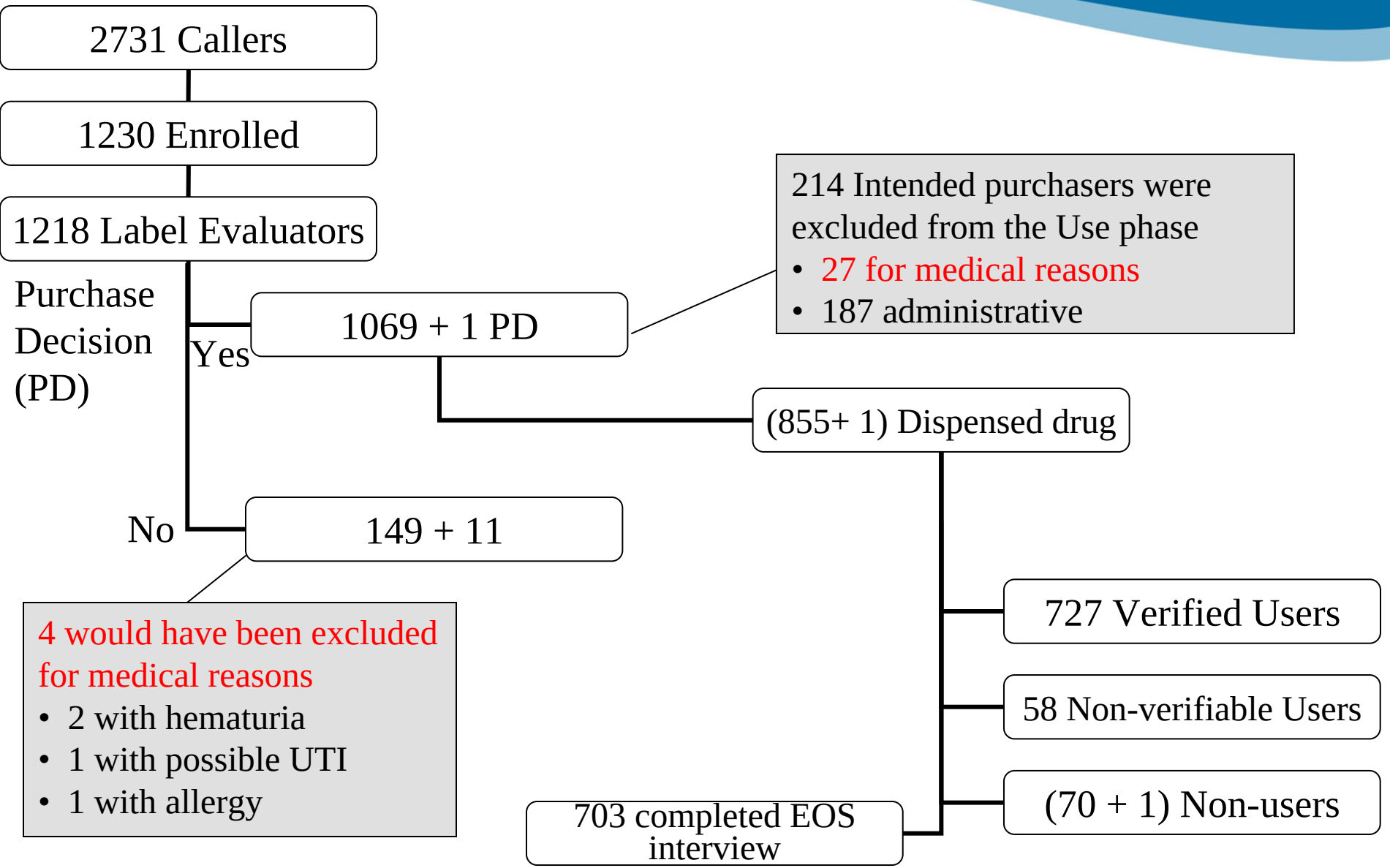
- Pregnant or breastfeeding
- Narrow-angle glaucoma
- Hematuria
- Fever or chills with OAB symptoms and either dysuria, hematuria, cloudy urine or foul-smelling urine
- Allergy to oxybutynin or ingredients

EOS = end-of-study

Subject Disposition



Subject Disposition



Purchase Decisions and Label Ineligibilities

Ineligibilities of Interest:

- Incomplete bladder emptying ("urinary retention"); 458/1069 (**42.8%**)
- Diabetes risk factors; 454/1069 (**42.4%**)
- Possible symptoms of UTI; 229/1069 (**21.4%**)
- Bladder cancer risk factors; 163/1069 (**15.2%**)
- Did not meet OAB symptom conditions; 138/1069 (**12.9%**)

- 21.5% (230/1069) of those interested in purchase (**PD = Yes**) were eligible as per the label; therefore
- 78.5% (839/1069) were ineligible as per the label

FINDINGS

Purchase decisions and label ineligibility

- Ineligible by indication for use (<2 symptoms; <3 months):

	PD = Yes N=1069	Dispensed Drug N=855	Users N=785	Users who Spoke with Doctor N=181
179	138	103	88	11

  - 13% (138/1069) of subjects making purchase decision (**PD = Yes**) did not meet the OAB symptom conditions
    - » Only 11% (88/785) of **users** did not meet the conditions

FINDINGS

Purchase decisions and label ineligibility

- Ineligible by indication for use (<2 symptoms; <3 months):

	PD = Yes N=1069	Dispensed Drug N=855	Users N=785	Users who Spoke with Doctor N=181
179	138	103	88	11

  - 12% (22/179) of **label evaluators** who were ineligible by the indication were told by their doctors that they had OAB.
    - » Eleven (11) used the drug.

FINDINGS

Primary and secondary endpoints

- Major endpoints related to misuse of Oxytrol for Women®
- Misuse by the primary endpoint and secondary endpoints 3 (SE3) and 5 (SE5) were mitigated
  - Mitigation strategies were reasonable, overall
- The Sponsor's misuse proportions
  - Primary: Based on total users of at least one patch
  - SE3: Based on users who used the drug for 2 weeks and completed the week 3 interview
  - SE5: Based on total users of at least one patch

FDA found these acceptable

- FDA considered additional proportions

Endpoints	Misuse – Pre-mitigation	
Primary Endpoint		
User had new or worsening symptoms, and failed to stop use/all users of at least one patch	**14.4%**	
(FDA) Same user who failed to stop use/all users with pertinent symptoms*	**74.5%**	**17.7%**
Secondary Endpoint 3		
User had no improvement and failed to stop use/all users of 2 weeks of drug	**22.6%**	**11%**
(FDA) Same user who failed to stop use/all users of 2 weeks with no improvement*	**77.5%**	**38%**
Secondary Endpoint 5		
Incorrect user (too long or too many TDSs)/all users of at least one patch	**51%**	**21%**

*FDA rates were exploratory, post-hoc, subgroup analyses

Primary Endpoint

Primary Endpoint	Pre-mitigation n=727 (%) (95% CI)	Post-mitigation n=727 (%) (95% CI)
Verified users who had symptoms indicating stopping use	141 (19.4%)	141 (19.4%)
Verified users who failed to stop use/ verified users of at least one patch	**14.4% (105/727)** (12%, 17.2%)	**3.4% (25/727)* (2.2%, 5%)**
Verified users who failed to stop use/ verified users who had symptoms indicating stopping use	74.5% (105/141) (66.4%, 81.4%)	17.7% (25/141) (11.8%, 25.1%)

***a priori* threshold rate for misuse: ≤ 5% (Upper Limit of 95% CI = 5%)**

Source: Adapted from sponsor's submission, Module 5.3.5.1, Section 11.1.1, Tables 13, 14 (p. 68, 69) and Tables 14-14-1 and 14-14-2.

Secondary Endpoint 3 (SE3)

Secondary Endpoint 3	Pre-mitigation N=643 (%) (95% CI)	Post-mitigation N=643 (%) (95% CI)
Total users who reported no improvement (stayed the same or worsened) after 2 weeks	187 (29.1%)	187 (29.1%)
Total users who failed to stop use/ all users who used the drug for 2 weeks	**22.6% (145/643) (19.4%, 26%)**	**11% (71/643) (8.7%, 13.7%)**
Total users who failed to stop use/ Total users who reported no improvement after 2 weeks	77.5% (145/187)	38% (71/187)

Source: Adapted from sponsor's submission, Module 5.3.5.1, Section 11.1.3, Table 18, p. 84

Secondary Endpoint 5 (SE5)

Secondary Endpoint 5	Pre-mitigation N=727 (%) (95% CI)	Post-mitigation N=727 (%) (95% CI)
Total users who incorrectly used (> 4 days and/or simultaneous use)	**370 (50.9%)**	**152 (20.9%)**
Total users who incorrectly used by duration only (> 4 days)	333 (45.8%)	155 (21.3%)
Total users who incorrectly used by simultaneous use only	77 (10.6%)	22 (3%)

- Misuse by either method 18.3% < 65 yrs; 28.6% > 75 yrs

Source: Adapted from sponsor's submission, Module 5.3.5.1, Section 11.1.7, Tables 40, 41 and 43

FINDINGS

- Safety
  - 66% of all users reported at least 1 adverse event (AE)
    - By age, no significant differences in reporting overall
    - AEs reported by > 2% of all users:
      - Application site irritation 18% (N=142)
      - UTI/cystitis 8.4% (N=66)
      - Dry mouth 4.1% (N=32)
      - Urge incontinence 3.1% (N=24)
      - Constipation 2.5% (N=17)
      - Back pain 2.3% (N=10)
  - 4.5% of all users had a serious AE; 1 death (viral pneumonia)
    - 2 or more reports: UTI* (5), stroke, back/chest pain, cholecystitis
  - 141 users (27.2% of all reporting AEs) discontinued due to AEs
    - 13 SAEs – only UTI (3), fractures (2), and stroke (2) more than once
    - Most common reasons were application site reactions

*** No clear reports of urosepsis**

SAEs = serious adverse events

Primary Safety Topics and Label Ineligibilities

- Possible symptoms of UTI
  - Fever or chills and
    - Dysuria
    - Hematuria
    - Back/ flank pain
    - Cloudy or foul-smelling urine
- Diabetes risk factors
  - Family history of diabetes
  - Excessive thirst, hunger or tiredness
- Incomplete bladder emptying, “urinary retention”
- Bladder cancer risk factors
  - Unexplained weight loss with
    - Dysuria, hematuria or back/ flank pain

FINDINGS

- Primary safety topics
  - Possible symptoms of UTI
    - 260 (21%) **label evaluators** and 154 (20%) **users** reported any possible symptoms of UTI (fever/chills or dysuria, or hematuria, or back/flank pain, or cloudy urine, or foul-smelling urine) at enrollment
      - only 3 who made a purchase decision (**PD = Yes**) were excluded for stricter UTI criteria
      - In total, 8 **users** were diagnosed with UTI during the trial
    - 26 (3%) **users** reported new, possible symptoms of UTI during trial
      - 15 correctly stopped using the drug
      - 4 were diagnosed with UTI

Label Evaluators N=1218	PD = Yes N=1069	Dispensed Drug N=855	Users N=785	
260	229	166	154	19

FINDINGS

- Primary safety topics
  - Possible symptoms of UTI
    - 5 **users** diagnosed with UTI had not met the OAB symptom conditions (< 2 symptoms; < 3 months duration)
      - None reported possible symptoms of UTI at enrollment
      - All recognized symptoms and sought prompt medical attention
      - Only 2.7% (33/1218) of **label evaluators** reported OAB symptoms < 1 month duration
    - 66 UTIs were diagnosed overall (5 SAEs)
      - Almost all users either recognized their symptoms or were diagnosed during routine health maintenance for other reasons
      - All 5 users with serious events reported long-term OAB symptoms
      - No apparent delays in diagnosis of UTI

FINDINGS

- Primary safety topics
  - Diabetes mellitus risk factors
    - Diabetes was diagnosed in 2 subjects; one user and one subject excluded for hematuria
    - Neither diagnosis appeared delayed due to their considered use of oxybutynin

Label Evaluators N=1218	PD = Yes N=1069	Dispensed Drug N=855	Users N=785	Users who Spoke with Doctor N=181
516	454	351	321	79

FINDINGS

- Primary safety topics
  - Feeling of incomplete bladder emptying, "urinary retention"
    - No cases of acute retention
      - 7 reports of new or worsening "retention"
      - None were SAEs, all were mild and self-resolved
      - One user discontinued on the advice of her doctor

Label Evaluators N=1218	PD = Yes N=1069	Dispensed Drug N=855	Users N=785	Users who Spoke with Doctor N=181
522	458	357	323	3

  - Bladder cancer risk factors
    - No cases of bladder cancer
    - No reports of delayed diagnosis in literature or other studies

FINDINGS

- Other safety topics
  - Allergy
    - 185 reported an AE describing allergy/hypersensitivity; 78 discontinued – most due to skin-related AEs
      - One SAE, but believed due to concomitant muscle relaxant, tizanidine
  - Skin reactions
    - 186 AEs reported by 177 users; 73 discontinued use
    - One SAE – skin blistering
      - Blistering occurred three months after user completed Use phase

FINDINGS

- Other safety topics
  - Anticholinergic effects
    - 105 AEs by 89 users
    - Dry mouth (32), constipation (20), dizziness/somnolence (29)
    - No SAEs; 25 discontinued use (dizziness or dry mouth)
    - 90% resolved or improved on follow up; none worsened
  - Disorientation and Confusion
    - Overlaps with CNS-related anticholinergic effects
    - 79 AEs by 78 users; 1 discontinued use
    - 2 SAEs (schizoaffective disorder and convulsive syncope)
  - Falls and accidents
    - May overlap with anticholinergic effects
    - 19 AEs by 17 users; 3 discontinued use
    - 7 SAEs; only 3 were in the Use phase, but none appeared related to CNS-anticholinergic effects

POSTMARKETING SAFETY DATA

POSTMARKETING SAFETY DATABASES

NDA holder's database

FDA-Adverse Event Reporting System (FDA-AERS)

World Health Organization (WHO)

American Association of Poison Control Centers

- 13,700 AEs reported worldwide since 2004
  - Included in NDA holder's database
  - Over 40 million TDS' distributed

POSTMARKETING TRIAL

MATRIX trial (sponsor-initiated trial to evaluate QoL measures)

QoL = quality of life

POSTMARKETING DATA (U.S.)

Findings are representative of worldwide data

- 8 AEs reported ≥ 2% of total; almost 40% - application site reactions
- 96% of all reports are non-serious; 0.7% serious, labeled

Organ System Class	Preferred Term	Serious Unlisted	Serious Listed	Non-Serious Unlisted	Non-Serious Listed	Total Events	% of Total Events
	Total # AEs:	**204**	**40**	**3,021**	**6,435**	**9,690**	
General Disorders & Administration Site Conditions	Application site erythema	0	0	0	1416	1416	**14.61%**
General Disorders	Application site pruritus	0	0	0	1053	1053	**10.87%**
General Disorders	Drug ineffective	0	0	359	601	960	**9.91%**
Gastrointestinal Disorders	Dry mouth	0	1	0	303	304	**3.14%**
General Disorders & Administration Site Conditions	Application site rash	0	0	0	246	246	**2.54%**
General Disorders & Administration Site Conditions	Application site irritation	0	0	1	220	221	**2.28%**
Eye Disorders	Vision blurred	0	0	0	196	196	**2.02%**
Nervous System Disorders	Dizziness	1	1	156	28	186	**1.92%**

Source: Adapted from Applicant's submission, Module 5.3.5.3, Section 3.5.2.1 Table 13, p. 74 (NDA holder's database)

Labeling

Additional concepts to consider

- Strengthen the sleepiness/dizziness/blurry vision warning (recent Rx update re: somnolence)
  - Consider the drug's use in an older population
  - Consumers may be taking other drugs with similar effects
- Additional warnings for anticholinergic effects, for example
  - Dry mouth
  - Constipation

} Not infrequently reported, and can be bothersome

Conclusions

- The CONTROL trial was adequately designed and populated.
- The sponsor met their primary endpoint.
  - Upper Limit of misuse rate = 5%
- The major endpoints and mitigation strategies were acceptable.
  - In total, 276 users (38% of verified users) developed new symptoms, or their OAB condition did not improve, indicating stopping use
    - 65 (23.5%; 65/276) talked to a doctor
      - 19 stopped use
      - 46 continued use

Conclusions

- Close to 80% of those who made a decision to purchase had any label ineligibility, and
- Some misuse and incorrect use analyses show that users may not always follow label directions and warnings; however
  - No apparent delayed diagnoses of more serious medical conditions with OAB symptoms (e.g., UTI and diabetes)
  - No concerning safety trends or signals identified in the trial
- Trial and postmarketing data indicates that application site reactions and anticholinergic effects are most common, but mostly non-serious